PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C12N 15/12, C07K 14/47, A61K 38/08, 38/10, 38/17, C12N 15/11, 15/86, C07K 16/18, C12Q 1/68, A61K 35/14, A01K 67/027, C12N 5/08

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60/061,428 8 October 1997 (08.10.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/061,428 (CIP)
Filed on 8 October 1997 (08.10.97)

(71) Applicant *(for all designated States except US)*: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: WANG, Rong, Fu [US/US]; 4949 Battery Lane #409, Bethesda, MD 20814 (US). ROSENBERG, Steven, A. [US/US]; 10104 Iron Gate Road, Potomac, MD 20854 (US).

(74) Agents: FEILER, William, S. et al.; Morgan & Finnegan, L.L.P., 345 Park Avenue, New York, NY 10154 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL HUMAN CANCER ANTIGEN NY ESO-1/CAG-3 AND GENE ENCODING SAME

(57) Abstract

The present invention discloses the identification, isolation and cloning of a gene encoding a novel cancer antigen NY ESO-1/CAG-3 and peptides thereof derived from various open reading frames from the NY ESO-1 gene. The novel cancer antigen and peptides are recognized by cytotoxic T lymphocytes in an HLA restricted manner. The products of the gene are promising candidates for immunotherapeutic strategies for the prevention, treatment and diagnosis of patients with cancer.

FOR THE PURPOSES OF INFORMATION ONLY

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2026-4269PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/19609	21/09/1998	08/10/1997
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THE GOVERNMENT OF THE UNITED STATES OF A. ..et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/04/1999	08.02.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Nichogiannopoulou, A Telephone No. +49 89 2399 8054

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/19609

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-62	as originally filed				)

Claims, No.:

2-24,26-49, 51-69	as received on	14/01/2000	with letter of	14/01/2000

Drawings, sheets:

1/16-16/16	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 1, 25, 50
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5, 14, 19, 22, 24-27, 31, 36-38, 41, 43-69
	No:	Claims	2-4, 6-13, 15-18, 20, 21, 23, 28-30, 32-35, 39, 40, 42
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-59, 65-69
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I
Basis of the report

1. This IPER was established based on the application documents and sequence listing pages 1-25.

Re Item II
Priority

1. The following documents were published prior to the international filing date but after the claimed priority date (P-documents):

   P1: WO 98 14464 A (LUDWIG INST CANCER RES) 9 April 1998
   P2: WO 98 32855 A (LUDWIG INST CANCER RES) 30 July 1998
   P3: JÄGER, E. et al.: 'Simultaneous humoral and cellular immune response against cancer-testis antigen NY-ESO-1: definition of human histocompatibility leukocyte antigen (HLA)-A2-binding peptide epitopes.' J. EX. MED., (19 January 1998), 187: 265-70

2. The priority document pertaining to the present application was not available at the time of establishing this IPER. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (08.10.1997). If it later turns out that this assumption is incorrect, P1-P3 will become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(1) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: CHEN, Y.T. et al.: 'A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening' PROC. NATL. ACAD. SCI., (March 1997), 94: 1914-1918
   D2: WO 97 29195 A (US HEALTH) 14 August 1997
   D3: PARKHURST, M.R. et al.: 'Improved induction of melanoma-reactive CTL with peptides from the melanoma antigen gp100 modified at HLA-A*0201-binding residues.' J. IMMUNOL., (1996), 157: 2539-48

2. The present application discloses the identification and cloning of cancer antigen gene 3 (CAG-3 or NY-ESO-1), a tumour antigen expressed on human melanoma and breast cancer cells. This antigen and peptides derived from it are recognised by cytotoxic T cells derived from TILs, in the context of HLA.

3. **Novelty** (Article 33(2) PCT)

3.1. D1 is the disclosure of the cloning of NY-ESO-1. Figure 3 on page 1917 of D1 discloses the nucleotide and amino acid sequences of NY-ESO-1 which share 100% identity with SEQ ID NOs: 1-3, 51, 54 and SEQ ID NOs: 4, 15, 25, 26, 45, respectively. D1 is thus detrimental to the novelty of claims 2-4, 6-13, 15-18, 20, 21, 23, 28, 29 and 32-35.

3.2. Immunogenicity is an inherent property of all antigenic peptides and can as such not be used to restore novelty of a known antigen. D1 is thus also detrimental to the novelty of claim 30.

3.3. Since the cloning and sequencing procedure inevitably includes transformation of host cells with recombinant expression vectors, D1 is also detrimental to the novelty of claims 39 and 40.

3.4. The ^{32}P-labelled probe used for Northern blot analysis in D1 (see page 1915, Materials and Methods section) is detrimental to the novelty of claim 42.

4. **Inventive step** (Article 33(3) PCT)

4.1. D2 teaches the phenomenon of different tumour antigens being encoded by different open reading frames of the same gene and the possible uses of tumour antigen sequences, e.g. recombinant viruses comprising such antigenic sequences. Given the disclosure of D1 of the cancer antigen NY-ESO-1 and the teachings of D2, no inventive step can be recognised in formulating present claims 5, 24, 26, 27, 31, 36-38, 41-48 and 53-66.

4.2. D3 teaches that tumour antigens can be rendered more immunogenic by amino acid modifications. In light of this disclosure, the subject-matter of claims 14, 19 and 22 is rendered obvious.

4.3. Techniques for obtaining antibodies are well known in the art, and antibodies can be obtained against any known peptide in a straightforward manner without the requirement of inventive skill. Accordingly the provision of antibodies against antigens that lack novelty and/or inventiveness cannot be regarded as inventive. Claims 49, 51 and 52 are thus found to lack an inventive step.

4.4. The same argumentation as under item 4.2. holds true for the generation of transgenic animals. Claim 66 is thus regarded as lacking an inventive step.

4.5. The same argumentation as under items 4.2. and 4.3. holds true for the generation of cytotoxic T lymphocytes. Claims 67-69 are thus regarded as lacking an inventive step.

5. **Industrial applicability** (Article 33(4) PCT)
Claims 60-64 -as they concern *in vivo* methods- relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re item VIII

Certain observations on the international application

1. The terms "derivative", "variant" and "analog" used in claims 1-11, 14-18, 24-27, 32 and 35 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

.TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 July 1999 (19.07.99)	
International application No. PCT/US98/19609	**Applicant's or agent's file reference**
International filing date (day/month/year) 21 September 1998 (21.09.98)	**Priority date** (day/month/year) 08 October 1997 (08.10.97)
Applicant WANG, Rong, Fu et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 April 1999 (02.04.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Catherine Massetti
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

Brown

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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To:

FEILER, William
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.02.00
Applicant's or agent's file reference 2026-4269PC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/19609	21/09/1998	08/10/1997

Applicant
THE GOVERNMENT OF THE UNITED STATES OF A. ..et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vullo, C Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2026-4269PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/19609	21/09/1998	08/10/1997
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   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/04/1999	08.02.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Nichogiannopoulou, A Telephone No. +49 89 2399 8054

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/19609

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-62	as originally filed				

Claims, No.:

2-24,26-49, 51-69	as received on	14/01/2000	with letter of	14/01/2000	

Drawings, sheets:

1/16-16/16	as originally filed				

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 1, 25, 50
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

Re Item I
Basis of the report

1. This IPER was established based on the application documents and sequence listing pages 1-25.

Re Item II
Priority

1. The following documents were published prior to the international filing date but after the claimed priority date (P-documents):

   P1: WO 98 14464 A (LUDWIG INST CANCER RES) 9 April 1998
   P2: WO 98 32855 A (LUDWIG INST CANCER RES) 30 July 1998
   P3: JÄGER, E. et al.: 'Simultaneous humoral and cellular immune response against cancer-testis antigen NY-ESO-1: definition of human histocompatibility leukocyte antigen (HLA)-A2-binding peptide epitopes.' J. EX. MED., (19 January 1998), 187: 265-70

2. The priority document pertaining to the present application was not available at the time of establishing this IPER. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (08.10.1997). If it later turns out that this assumption is incorrect, P1-P3 will become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(1) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: CHEN, Y.T. et al.: 'A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening' PROC. NATL. ACAD. SCI., (March 1997), 94: 1914-1918
   D2: WO 97 29195 A (US HEALTH) 14 August 1997
   D3: PARKHURST, M.R. et al.: 'Improved induction of melanoma-reactive CTL with peptides from the melanoma antigen gp100 modified at HLA-A*0201-binding residues.' J. IMMUNOL., (1996), 157: 2539-48

2. The present application discloses the identification and cloning of cancer antigen gene 3 (CAG-3 or NY-ESO-1), a tumour antigen expressed on human melanoma and breast cancer cells. This antigen and peptides derived from it are recognised by cytotoxic T cells derived from TILs, in the context of HLA.

3. **Novelty** (Article 33(2) PCT)

3.1. D1 is the disclosure of the cloning of NY-ESO-1. Figure 3 on page 1917 of D1 discloses the nucleotide and amino acid sequences of NY-ESO-1 which share 100% identity with SEQ ID NOs: 1-3, 51, 54 and SEQ ID NOs: 4, 15, 25, 26, 45, respectively. D1 is thus detrimental to the novelty of claims 2-4, 6-13, 15-18, 20, 21, 23, 28, 29 and 32-35.

3.2. Immunogenicity is an inherent property of all antigenic peptides and can as such not be used to restore novelty of a known antigen. D1 is thus also detrimental to the novelty of claim 30.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5, 14, 19, 22, 24-27, 31, 36-38, 41, 43-69
	No:	Claims	2-4, 6-13, 15-18, 20, 21, 23, 28-30, 32-35, 39, 40, 42
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-59, 65-69
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

3.3. Since the cloning and sequencing procedure inevitably includes transformation of host cells with recombinant expression vectors, D1 is also detrimental to the novelty of claims 39 and 40.

3.4. The ^{32}P-labelled probe used for Northern blot analysis in D1 (see page 1915, Materials and Methods section) is detrimental to the novelty of claim 42.

4. **Inventive step** (Article 33(3) PCT)

4.1. D2 teaches the phenomenon of different tumour antigens being encoded by different open reading frames of the same gene and the possible uses of tumour antigen sequences, e.g. recombinant viruses comprising such antigenic sequences. Given the disclosure of D1 of the cancer antigen NY-ESO-1 and the teachings of D2, no inventive step can be recognised in formulating present claims 5, 24, 26, 27, 31, 36-38, 41-48 and 53-66.

4.2. D3 teaches that tumour antigens can be rendered more immunogenic by amino acid modifications. In light of this disclosure, the subject-matter of claims 14, 19 and 22 is rendered obvious.

4.3. Techniques for obtaining antibodies are well known in the art, and antibodies can be obtained against any known peptide in a straightforward manner without the requirement of inventive skill. Accordingly the provision of antibodies against antigens that lack novelty and/or inventiveness cannot be regarded as inventive. Claims 49, 51 and 52 are thus found to lack an inventive step.

4.4. The same argumentation as under item 4.2. holds true for the generation of transgenic animals. Claim 66 is thus regarded as lacking an inventive step.

4.5. The same argumentation as under items 4.2. and 4.3. holds true for the generation of cytotoxic T lymphocytes. Claims 67-69 are thus regarded as lacking an inventive step.

5. **Industrial applicability** (Article 33(4) PCT)
Claims 60-64 -as they concern *in vivo* methods- relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re item VIII

Certain observations on the international application

1. The terms "derivative", "variant" and "analog" used in claims 1-11, 14-18, 24-27, 32 and 35 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

WE CLAIM:

2. A cancer peptide, functional portion or derivative wherein the peptide is encoded by a nucleic acid sequence consisting of a portion of SEQ. ID NO: 2, wherein said portion encodes a peptide immunologically recognized by antigen specific cytotoxic T lymphocytes.

3. A cancer peptide, functional portion or derivative thereof wherein the peptide is encoded by a nucleic acid sequence consisting of SEQ. ID NO: 3 or portion thereof.

4. A cancer peptide consisting of a portion of SEQ. ID NO: 4 or derivative thereof, wherein said portion is immunologically recognized by antigen specific cytotoxic T lymphocytes.

5. A cancer peptide consisting of SEQ. ID NO: 5 or portion or derivative thereof.

6. A cancer peptide, portion or derivative thereof according to claim 2-4 or 5 wherein the cancer peptide is immunologically recognized by HLA restricted cytotoxic T lymphocytes.

7. A cancer peptide, portion or derivative thereof according to claim 2-4 or 5 wherein the cytotoxic T lymphocytes are MHC class I restricted.

8. A cancer peptide, portion or derivative thereof according to claim 2-6 or 7 wherein the cancer peptide is derived from a cancer selected from the group consisting of: a non-Hodgkins lymphoma, leukemia, Hodgkins lymphoma, lung cancer, liver cancer, metastases, melanoma, adenocarcinoma, thymoma, colon cancer, uterine cancer, breast cancer, prostate cancer, ovarian cancer, cervical cancer, bladder cancer, kidney cancer, pancreatic cancer and sarcoma.

9. A cancer peptide, portion or derivative thereof according to claim 2-7 or 8 wherein the cancer peptide or portion thereof is present on primary breast tumor isolates and melanoma cells.

10. A cancer peptide, portion or derivative thereof according to claim 2 wherein the peptide is encoded by a nucleic acid sequence consisting of SEQ. ID NO: 51.

11. A cancer peptide, portion or derivative thereof according to claim 2 wherein the cancer peptide consists of the amino acid sequence:

ASGPGGGAPR (SEQ ID NO. 25), or derivative thereof.

12. A cancer peptide according to claim 11, further consisting of an addition of 1 to about 10 amino acids at the N-terminus of SEQ. ID NO: 25.

13. A cancer peptide according to claim 11, further consisting of an addition of 1 to about 5 amino acids at the N-terminus of SEQ. ID NO: 25.

14. The cancer peptide, portion or derivative thereof according to claim 2 wherein the cancer peptide consists of the amino acid sequence:

ASGPGGGAPK (SEQ. ID NO: 39).

15. The cancer peptide, portion or derivative thereof according to claim 2 wherein the cancer peptide consists of the amino acid sequence:

AGAARASGPGGGAPR (SEQ. ID NO: 26)

16. The cancer peptide, portion or derivative thereof according to claim 2 wherein the cancer peptide consists of the amino acid sequence:

RGPRGAGAARASGPGGGAPR (SEQ. ID NO: 45).

17. A cancer peptide, portion or derivative thereof according to claim 2 wherein the cancer peptide consists of the amino acid sequence:

TVSGNILTIR (SEQ. ID NO: 15).

18. A cancer peptide or analog thereof consisting of the amino acid sequence:

Xaa_1Xaa_2 Xaa_3GPGGGAPXaa_4 wherein Xaa_1 is no amino acid or one to 10 amino acids, Xaa_2 is Ala, Thr, Val, Leu or Arg, Xaa_3 is Ser or a conservative amino acid substitution, and Xaa_4 is Arg or Lys.

19. The cancer peptide according to claim 18 wherein the conservative amino acid at Xaa_3 is selected from the group consisting of Ala, Val, Ile, Leu and Thr.

20. The cancer peptide according to claim 18 wherein Xaa_1 is at least one amino acid selected from the group consisting of Ala, Gly, Arg or combinations thereof.

21. The cancer peptide according to claim 18 wherein Xaa_2 is Ala, Val or Thr.

22. The cancer peptide according to claim 18 wherein Xaa_2 is Arg.

23. The cancer peptide according to claim 18 wherein Xaa_4 is Arg and Xaa_1 is one to 5 amino acids selected from the group consisting of Ala, Gly, Arg or combinations thereof.

24. A cancer peptide, portion or derivative thereof encoded by an alternative open reading frame consisting of SEQ. ID NO. 3, variant or homolog thereof

26. A cancer peptide, portion or derivative thereof according to claim 24 wherein the peptide comprises the amino acid sequence:

LAAQERRVPR (SEQ. ID NO: 47).

27. A cancer peptide, portion or derivative thereof according to claim 24 wherein the peptide comprises the amino acid sequence:

AAQERRVPR (SEQ. ID NO: 46).

28. A pharmaceutical composition comprising at least one cancer peptide according to claims 2-24, 26 or 27 and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition consisting essentially of a peptide having a portion of SEQ. ID NO. 4, said portion is immunologically recognized by antigen specific cytotoxic T lymphocytes, a peptide having SEQ. ID NO: 5, SEQ. ID NO: 14, SEQ. ID NO: 25, SEQ. ID NOS: 34-38, 41, 42, 46, 47 or combinations thereof and a pharmaceutically acceptable carrier.

30. A immunogen comprising the cancer peptide according to claims 2-24, 26 or 27 alone or in combination with at least one immunostimulatory molecule, said immunogen elicits antigen specific cytotoxic T lymphocytes.

31. A immunogen according to claim 30 wherein the

immunostimulatory molecule is an HLA molecule.

32. An isolated nucleic acid sequence consisting of a portion of SEQ ID NO: 2, or homolog thereof, wherein said portion encodes a peptide immunologically recognized by antigen specific cytotoxic T lymphocytes.

33. An isolated nucleic acid sequence consisting of SEQ ID NO.: 3 or portion or variant thereof.

34. An isolated nucleic acid sequence according to claim 33 wherein the nucleic acid sequence encodes an alternative open reading frame gene product.

35. An isolated nucleic acid sequence according to claim 32 wherein the sequence encodes an amino acid sequence:

ASGPGGGAPR (SEQ ID NO.: 25), or derivative thereof.

36. An isolated nucleic acid sequence encoding the ORF2 peptide of SEQ. ID NO: 5.

37. An isolated nucleic acid sequence according to claim 36 wherein the nucleic acid sequence encodes a cancer peptide having the amino acid sequence:

LAAQERRVPR (SEQ. ID NO: 47).

38. An isolated nucleic acid sequence according to claim 36 wherein the nucleic acid sequence encodes a cancer peptide having the amino acid sequence:

AAQERRVPR (SEQ. ID NO: 46).

39. A recombinant expression vector comprising the nucleic acid sequence according to claims 32-37 or 38.

40. A host organism transformed or transfected with a recombinant expression vector according to claim 39.

41. A host organism according to claim 40 wherein the host organism is an antigen presenting cell.

42. An oligonucleotide consisting of a nucleic acid sequence complementary to the nucleic acid sequence according to claims 32-37 or 38.

43. A recombinant virus comprising a recombinant virus which has incorporated into a viral genome or portion thereof the nucleic acid sequence according to claims 32-37 or 38.

44. A recombinant virus according to claim 43 further comprising at least one gene encoding an immunostimulatory molecule.

45. The recombinant virus according to claim 43 wherein the virus is selected from the group consisting of retrovirus, baculovirus, Ankara virus, fowlpox, adenovirus, and vaccinia virus.

46. The recombinant virus according to claim 43 wherein the cancer peptide is derived from melanocytes.

47. A recombinant virus according to claim 44 wherein the immunostimulatory molecule is a HLA class I molecule.

48. A host organism transformed or transfected with the recombinant virus according to claim 43-46 or 47.

49. An isolated antibody or antigen binding portion thereof that binds the cancer peptide, or portion thereof encoded by SEQ. ID NO: 3.

51. An isolated antibody that binds a cancer antigen consisting of SEQ ID NOS: 5, 6, 14, 25, 34-38, 41, 42, 46, 47 or a fragment thereof.

52. An isolated antibody that binds the cancer peptide, antigen or variant thereof of claim 11.

53. A method of producing a recombinant cancer peptide or portion thereof comprising:

a. inserting a nucleotide sequence of SEQ ID NO.: 3

or portion or variant thereof, or a portion or variant of SEQ ID NO. 2, into an expression vector;

b. transferring the expression vector into a host cell;

c. culturing the host cell under conditions appropriate for expression of the cancer peptide or portion thereof; and

d. harvesting the recombinant cancer peptide, or portion thereof.

54. A method according to claim 53 further comprising in step (a) inserting a nucleotide sequence encoding an HLA class I molecule, or portion thereof into the expression vector.

55. A method of detecting the presence of cancer or precancer in a mammal comprising:

a. contacting a nucleic acid sequence of SEQ ID NO.: 3 or portion or variant thereof, or a portion of SEQ ID NO. 2 with a test biological sample of mRNA taken from the mammal under conditions allowing for a complex to form between the sequence and the mRNA;

b. detecting the complex;

c. comparing the amount of mRNA in the test sample with an amount of mRNA from a known normal biological sample, wherein an increased amount of mRNA from the test sample is indicative of cancer or precancer.

56. A method according to claim 55 wherein the cancer or precancer is melanoma.

57. A method according to claim 55 wherein the biological sample is from breast tissue.

58. A method of detecting an CAG-3 genomic nucleic acid sequence in a biological sample comprising:

a. contacting the genomic nucleic acid sequence with SEQ

ID NO.: 3, 51, or portion or variant thereof under conditions to allow complexes to form between the genomic nucleic acid sequence; and

b. detecting the complex.

59. A method of detecting the cancer peptide or portion thereof according to claims 2-24, 26 or 27 in a biological sample comprising:

a. contacting the sample with antibodies specific for said cancer peptide under conditions to form an immune complex, and

b. detecting the presence of the immune complex.

60. A method of preventing or inhibiting cancer in a mammal comprising: administering to the mammal an effective amount of the cancer peptide, or portion thereof according to claims 2-24, 26 or 27, alone or in combination with an HLA molecule, said amount is effective in preventing or inhibiting the cancer in the mammal

61. A method of inhibiting melanoma in a mammal comprising:

a. exposing T lymphocytes *in vitro* to a cancer peptide, tumor antigen or portion thereof according to claims 2-24, 26 or 27, alone or in combination with an MHC molecule for a time sufficient to elicit cancer peptide specific T lymphocytes;

b. administering the cancer peptide specific T lymphocytes to the mammal in an amount sufficient to inhibit the melanoma.

62. A method of preventing or inhibiting cancer in a mammal comprising administering to the mammal an effective amount of the cancer peptide according to claims 2-24, 26 or 27 alone, or in combination with an HLA molecule, said amount is effective in preventing or inhibiting cancer in a mammal.

63. A method of preventing or inhibiting cancer in a mammal comprising administering to the mammal an effective amount of a recombinant virus according to claims 43-46 or 47 alone or in combination with an exogenous immunostimulatory molecule said amount is effective in preventing or inhibiting the cancer.

64. A method according to claim 63 wherein the mammal expresses an HLA Class I molecule selected from the group consisting of HLA-A31, HLA-A3, HLA-A11, HLA-A33, or HLA-A68.

65. A pharmaceutical composition comprising the recombinant virus according to claims 43-46 or 47 alone or in combination with an exogenous immunostimulatory molecule, chemotherapy drug, antibiotic, antifungal drug, antiviral drug or combination thereof and a pharmaceutically acceptable carrier.

66. A transgenic animal carrying and expressing a gene consisting of SEQ ID NO: 3 or portion thereof, or a portion of SEQ ID NO. 2, wherein said portion encodes a peptide immunologically recognized by antigen specific cytotoxic T lymphocytes

67. A cancer antigen specific human cytotoxic T lymphocyte elicited by the cancer peptide according to claim 2-24, 26 or 27.

68. The cancer antigen specific human cytotoxic T lymphocyte according to claim 67, wherein the lymphocyte recognizes an HLA-A31 molecule.

69. The cancer antigen specific human cytotoxic T lymphocyte according to claim 67; wherein the lymphocyte recognizes an HLA Class I molecule selected from the group consistingof HLA-A3, HLA-A11, HLA-A33, and HLA-A68.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 19609	International filing date *(day/month/year)* 21/09/1998	(Earliest) Priority Date *(day/month/year)* 08/10/1997
Applicant THE GOVERNMENT OF THE UNITED STATES OF A. ..et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

HUMAN CANCER ANTIGEN NY ESO-1/CAG-3 AND GENE ENCODING SAME

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/19609

Box I Obs rvati ns where rtain laims were f und uns archable (C ntinuati n f item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 60-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/ composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 4,11-23,32-35,52,58 to completion and 1-3,6-10, 28-31,39-51,53-57,59-69 partially

A cancer peptide comprising seq.ID 4 or portion or derivative thereof, pharmaceutical composition comprising said peptide(s), immunogen comprising one of said peptides, nucleic acids encoding said peptide and portions thereof, expression vector comprising said nucleic acid sequence, host comprising said vector, and method of production of said protein using said host. Also an antibody binding to said protein, a method for detecting the presence of cancer involving assessment of the level of mRNA which encodes said protein, a transgenic animal expressing said protein, a human cytotoxic T-lymphocyte elicited by said protein, and a recombinant virus encoding said protein and optionally an immunostimulatory molecule or a HLA class I molecule, and pharmaceutical compositions of said virus.

2. Claims: 5,24-27,36-38 to completion and 1-3,6-10,28-31, 39-51,53-57,59-69 partially

A cancer peptide comprising seq.ID 5 or portion or derivative thereof, pharmaceutical composition comprising said peptide(s), immunogen comprising one of said peptides, nucleic acids encoding said peptide and portions thereof, expression vector comprising said nucleic acid sequence, host comprising said vector, and method of production of said protein using said host. Also an antibody binding to said protein, a method for detecting the presence of cancer involving assessment of the level of mRNA which encodes said protein, a transgenic animal expressing said protein, a human cytotoxic T-lymphocyte elicited by said protein, and a recombinant virus encoding said protein and optionally an immunostimulatory molecule or a HLA class I molecule, and pharmaceutical compositions of said virus.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

It has been noticed that seq.ID 4 is not a true translation of seq.ID 1 and/or seq.ID 2; the latter nucleic acid sequences comprise the argenine encoding codon AGA at bp positions 214-216 of seq.ID 1, whereas the amino acid sequence described in seq.ID 4 comprises a proline residue at the corresponding amino acid - position 43. The search has been carried out for both possibilities.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/19609

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 A61K38/08 A61K38/10 A61K38/17
C12N15/11 C12N15/86 C07K16/18 C12Q1/68 A61K35/14
A01K67/027 C12N5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K C12Q A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN Y -T ET AL: "A TESTICULAR ANTIGEN ABERRANTLY EXPRESSED IN HUMAN CANCERS DETECTED BY AUTOLOGOUS ANTIBODY SCREENING" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, March 1997, pages 1914-1918, XP002064909	1-4, 6-13, 15-18, 20,21, 23,28, 29,32-35
Y	see figure 3	30,31, 39-48, 53-66

Y	WO 97 29195 A (US HEALTH) 14 August 1997	30,31, 39-48, 53-66
	see whole document, particularly the claims.	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 1999	04.06.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Smalt, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	VAN ELSAS, A. ET AL.: "Transformation of IL-2 augments CTL response to human melanoma cells in vitro: immunological characterization of a melanoma vaccine." JOURNAL OF IMMUNOTHERAPY, vol. 20, no. 5, September 1997, pages 343-53, XP002096030	28-31, 60,62, 67-69
A	see abstract; figures 6B,7	40,41, 48,53, 54,59,61
A	PARKHURST, M.R. ET AL.: "Improved induction of melanoma-reactive CTL with peptides from the melanoma antigen gp100 modified at HLA-A*0201-binding residues." JOURNAL OF IMMUNOLOGY, vol. 157, 1996, pages 2539-48, XP002096010 see the whole document	
P,X	WO 98 14464 A (LUDWIG INST CANCER RES) 9 April 1998 see whole document, particularly the claims	1-4, 6-13, 15-18, 20,21, 23, 28-35, 39-41, 43-63, 65,67
P,X	WO 98 32855 A (GODELAINE DANIELE ;LETHE BERNARD (BE); LUCAS SOPHIE (BE); SMET CHA) 30 July 1998 see whole document, particularly the claims	1-4, 6-13, 15-18, 20,21, 23, 28-35, 39-42, 53-62, 65,67
P,X	JÄGER, E. ET AL.: "Simultaneous humoral and cellular immune response against cancer-testis antigen NY-ESO-1: definition of human histocompatibility leukocyte antigen (HLA)-A2-binding peptide epitopes." JOURNAL OF EXPERIMENTAL MEDICIN, vol. 187, no. 2, 19 January 1998, pages 265-70, XP002096011 see abstract; figure 3	49-52,67

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/19609

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729195 A	14-08-1997	US 5840839 A	24-11-1998
		US 5831016 A	03-11-1998
		AU 1957297 A	28-08-1997
		EP 0882130 A	09-12-1998
WO 9814464 A	09-04-1998	US 5804381 A	08-09-1998
		AU 4349597 A	24-04-1998
WO 9832855 A	30-07-1998	US 5811519 A	22-09-1998
		AU 6042198 A	18-08-1998